

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

NATURAL ALTERNATIVES)	
INTERNATIONAL, INC., ET AL.,)	
)	
Plaintiffs,)	
)	
v.)	C.A. No. 09-626-GMS
)	
VITAL PHARMACEUTICALS, INC., and DNP)	
INTERNATIONAL CO., INC.,)	
)	
Defendants.)	
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VITAL PHARMACEUTICALS, INC.,)	
)	
Counterclaim / Third-Party Plaintiff,)	
)	
v.)	
)	
NATURAL ALTERNATIVES)	
INTERNATIONAL, INC., and COMPOUND)	
SOLUTIONS, INC.,)	
)	
Counterclaim / Third-Party Defendants.)	
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DEFENDANTS' ANSWERING CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

Motivated by this litigation, Plaintiffs ask the Court to re-write the at-issue claims to give them meaning that is neither ordinary nor supported by the intrinsic evidence. Plaintiffs' constructions fly in the face of the canons of claim construction and should be rejected. Defendants' constructions, on the other hand, are compelled by the intrinsic record. The Court should adopt Defendants' constructions in their entirety.

II. CONSTRUCTION OF THE DISPUTED TERMS

A. The Construction of "Beta-Alanine" and "L-histidine" Should Not Be Limited to the Individual Amino Acid Form

Plaintiffs' Proposed Construction	Defendants' Proposed Construction
<p>"beta alanine" means "the individual amino acid, beta-alanine, or its salt, ester or amide"</p> <p>"L-histidine" means "the individual amino acid, L-histidine, or its salt, ester, or amide"</p>	<p>"beta alanine" means "beta-alanine in the form of the individual amino acid, or as a component of a dipeptide (such as carnosine), an oligopeptide, or a polypeptide, or an active derivative thereof"</p> <p>"L-histidine" means "L-histidine in the form of the individual amino acid, or as a component of a dipeptide (such as carnosine), an oligopeptide, or a polypeptide, or an active derivative thereof"</p>

Plaintiffs' constructions of "beta-alanine" and "L-histidine" are starkly inconsistent with what Plaintiffs *admit* are the inventors' *definitions*. In contrast, Defendants' constructions *are* the inventors' definitions.

1. The Specification Provides a Single Express Definition of Both "Beta-Alanine" and "L-Histidine"

The inventors defined the terms "beta-alanine" and "L-histidine" in the specification:

Each of the beta-alanine or L-histidine can be in the form of the individual amino acids, or components of dipeptides, oligopeptides, or polypeptides. The beta-alanine can be active derivatives.

‘361 Patent (J.A. Ex. 3) at col. 2, Ins. 43-46. Defendants adopt the inventors’ definition virtually verbatim in their proposed construction. Plaintiffs, on the other hand, would have this Court reject the inventors’ definition and limit the terms “beta-alanine” and “L-histidine” to only the “individual” amino acid or its salt, ester, or amide. The claims, specification, prosecution history, and extrinsic evidence, however, preclude Plaintiffs’ efforts.

Plaintiffs do not dispute that the inventors *defined* the terms “beta-alanine” and “L-histidine” in the passage of the specification set forth above. *See* Plaintiffs’ Opening Brief (OB) at 11 (discussing “the definition of β -alanine and L-histidine in the specification”). Instead, Plaintiffs contend that this passage of the specification provides “multiple definitions” for those terms, citing *Genentech, Inc. v. Wellcome Foundation, Ltd.*, 29 F.3d 1555 (Fed. Cir. 1994). Plaintiffs’ argument fails. This case is nothing like *Genentech*, where the Federal Circuit found that the specification contained *four diverse and distinct definitions of “t-PA”*—three different structural definitions and a fourth functional definition. *Genentech*, 29 F.3d at 1563-64. Here, the patent specification provides a single definition for “beta-alanine” and “L-histidine.” That definition makes clear that “beta-alanine” and “L-histidine” are not limited to beta-alanine and L-histidine in the form of the individual amino acid (free form), but also includes the amino acids as components of dipeptides, oligopeptides, or polypeptides (bound form), as well as active derivatives. Plaintiffs do not explain how the express definition of beta-alanine and L-histidine can be read as constituting “multiple definitions.” It is a single, internally consistent definition.

2. Plaintiffs’ Technical Explanations Support Defendants’ Construction

Plaintiffs’ own explanations of dipeptides and amino acids further confirm that beta-alanine and L-histidine can be found as components of dipeptides. Plaintiffs concede that “[d]ipeptides, tripeptides, oligopeptides and polypeptides all contain more than one amino acid.” Plaintiffs’ OB at 2. Plaintiffs also concede that carnosine, also known as beta-analythistidine, is

a dipeptide. *Id.* at 1 n.2. It thus follows that the dipeptide carnosine contains two amino acids: beta-alanine and L-histidine.¹ In other words, carnosine contains beta-alanine “as a component of a dipeptide.” This is precisely what the definition of beta-alanine in the specification allows, and it is correctly captured in Defendants’ proposed construction.²

Similarly, Plaintiffs’ rely upon the inventors’ own publications in their brief—yet those publications use the terms “beta-alanine” and “L-histidine” in a way that encompasses beta-alanine and L-histidine in the form of the individual amino acid *or as components of dipeptides*. See Harris, *et. al.*, cited at Plaintiff’s OB at n.1, at pg. 280 (referring to “β-alanine in the form of anserine and carnosine”) (Walter Decl. (D.I. 78) Ex. C).

3. The Applicants Did Not Clearly and Unmistakably Disavow the Specification’s Definition of “Beta-Alanine” and “L-Histidine”

Plaintiffs excerpt a single statement from the file history of the ‘596 patent and argue that it evidences a “disavowal” of beta-alanine and L-histidine in the form of components of dipeptides. Plaintiffs’ OB at 11. Not only does the ‘596 patent file history fail to support such a disavowal, but the file histories and claims of the other patents-in-suit and related applications make clear that no such disavowal occurred.

¹See also Declaration of Dr. Malcolm Watford (D.I. 79) at ¶ 9 (“A dipeptide is a molecule consisting of two amino acids linked together by a peptide bond. For example carnosine, which is used throughout the patents-in-suit and also referred to as beta-alanyl-L-histidine and beta-alanylhistidine, is a dipeptide consisting of the amino acids beta-alanine and L-histidine bound by a peptide bond.”).

² In addition, the “individual amino acid” form of beta-alanine is only one form of beta-alanine. Claim 1 of the ‘361 patent recites the phrase “selected from the group consisting of *a* beta-alanine, an ester of *a* beta-alanine and an amide of *a* beta-alanine.” ‘361 patent, col. 15, lns. 18-21. The indefinite article “a” contemplates the possibility of multiple forms of beta-alanine. However, under Plaintiffs’ construction, there would only be one form of beta-alanine, the individual form. Thus, Plaintiffs’ construction cannot be reconciled with the language of claim 1. Other claims in the ‘361 patent recites “a beta-alanine” in the same fashion. See ‘361 patent claims 1, 5, 10, 17, 22, 27, and 33.

a. The Petition to Make Special in the ‘596 Patent File History Does Not Exclude “Beta-Alanine” and “L-Histidine” as Components of Dipeptides

Plaintiffs misinterpret the applicants’ statement in the Petition to Make Special to be a disavowal of the specification’s express definition of beta-alanine and L-histidine. In the statement, the inventors contrast their invention to *Setra* on the basis that *Setra* “teaches dipeptides.” J.A. Ex. 4. In other words, the applicants noted that *Setra* focused on dipeptides, while their invention related to the beta-alanine and L-histidine (which can be in the *form* of the individual amino acid, or in the *form of a component* of a dipeptide, oligopeptide, or polypeptide, or an active derivative thereof). Accordingly, the inventors’ statement that “in contrast to the present invention, the compositions and methods described in *Setra*’s invention teaches dipeptides” *has nothing to do with disclaiming any portion of the definition of beta-alanine and L-histidine set forth in the specification*. Similarly, the applicants’ statement that “*Setra* does not teach, suggest, or mention using mono peptides for the treatment of hydronium ions” merely characterizes the *Setra* reference. Again, there is no disclaimer of the specification’s definition of beta-alanine and L-histidine.

Additional proof that the Petition to Make Special did not disclaim dipeptides (or beta-alanine and L-histidine as components of dipeptides) is found in the “The Invention” section of that very same Petition to Make Special, wherein the applicants *expressly stated that their invention includes dipeptides, peptides, or peptide analogues*:

The methods of the present invention include providing *dipeptides, peptides or peptide analogues* by any number of means including, for example, ingestion and injection.

J.A. Ex. 4, March 4, 1999 Petition to Make Special at 3 (emphasis added). Thus, Plaintiffs’ argument that the Petition to Make Special evidences “a clear and mistakable disavowal that the

applicants' invention encompassed dipeptides" (Plaintiffs' OB at 10) is flat-out wrong and clearly contradicted by the record.

b. The Prosecution History as a Whole Indicates That the Invention Does Not Exclude Dipeptides

In addition to the Petition to Make Special in the '596 patent's file history, statements made by the inventors in the subsequent '361 patent, as well as in other subsequent patents, confirm there was no clear and unmistakable disavowal of beta-alanine and L-histidine as components of dipeptides. The terms "beta-alanine" and "L-histidine" are also used in these other patents, which share a common ancestor application, thus the Court should examine these related patents, including the patents' claims, specifications, and prosecution history, in construing the terms "beta-alanine" and "L-histidine." *See, NTP, Inc. v. Research in Motion, Ltd.*, 418 F. 3d 1282, 1293 (Fed. Cir. 2005) ("Because NTP's patents all derive from the same parent application and share many common terms, we must interpret the claims consistently across the asserted patents.") (citations omitted); *Jonsson v. Stanley Works*, 903 F.2d 812, 818 (Fed. Cir. 1990) (prosecution histories of patents in the same family are relevant to an understanding of the term in both patents).

In this case, the inventors applied for and were granted claims that contained the terms "beta-alanine" and "L-histidine" during the prosecution of the '361 patent (which occurred after the '596 patent prosecution). The '361 patent claims priority to the '596 patent, and both have identical disclosures. During the prosecution of the '361 patent, claims 1 and 3 were amended to encompass beta-alanine as a component of dipeptides *after* the Petition to Make Special was filed in the '596 patent. New claims 1 and 3 were added, and dependent claim 3 expressly claims a composition "wherein the beta-alanine further comprises a dipeptide, an oligopeptide, or a polypeptide." '361 patent, claims 3. In other words, dependent claim 3 *requires* that beta-

alanine be in the form of a component of a dipeptide, an oligopeptide, or a polypeptide. *Thus, the Petition to Make Special could not have been an express disclaimer of dipeptides; the inventors expressly claimed dipeptides.* Indeed, Plaintiffs’ construction of “beta-alanine” and “L-histidine” would render claim 3 nonsensical and internally inconsistent. If “beta-alanine” were limited to the individual amino acid form of beta-alanine (as Plaintiffs urge), then it could not “further comprise a dipeptide.” Moreover, the inventors expressly relied upon the specification’s definitional passage for the terms “beta-alanine” and “L-histidine” as support for both claims 1 and 3 when they were added by amendment. *See* J.A. Ex. 5, August 3, 2001 Response and Amendment at 7. This demonstrates that, in the Petition to Make Special, the applicants did not “disclaim” the patent’s express definition—because *the applicants later relied on that very same express definition.*

Accordingly, the subsequent actions of the inventors (by filing for claims in the related ‘361 patent encompassing dipeptides) and the Examiner (by allowing the claims encompassing dipeptides) further demonstrate that both the inventors and the Examiner understood there to be no disavowal of beta-alanine and L-histidine as components of dipeptides.

c. Later Patents in the Same Family Indicate That the Invention Does Not Exclude Dipeptides

The inventors also continued to use the definition of beta-alanine and L-histidine found in the specification of the patents-in-suit in the specification of later filed continuation-in-part applications. In those later applications, the inventors revised the specification, but continued to define beta-alanine and L-histidine as being in the form of either the individual amino acid or as components of dipeptides. For example, the specification’s of U.S. Patent Nos. 7,504,376 (“the ‘376 patent”) and 7,825,084 (“the ‘084 patent”) state as follows:

Each of the beta-alanine and/or L-histidine can be formulated or administered as individual amino acids, or, as components of dipeptides (e.g., carnosine, anserine,

and/or balenine), oligopeptides, or polypeptides. The beta-alanine, L-histidine, carnosine, anserine, and/or balenine, or peptides of beta-alanine can be active derivatives.

‘376 patent at col. 4, lns. 60-66, ‘084 patent at col. 4, ln. 67 – col. 5 ln. 6.³

The inventors also continued to submit claims directed to dipeptides in those related applications. For example, the original application as filed in the ‘376 patent included claims to beta-alanylhistidine dipeptide that also referred to beta-alanylhistidine dipeptide as beta-alanine.

Original claim 1 in the ‘376 patent application reads as follows:

1. A method of increasing anaerobic working capacity in a tissue comprising the following steps:
 - (a) providing a **beta-alanylhistidine dipeptide** and a glycine, an insulin, an insulin mimic, or an insulin-action modifier; and
 - (b) administering the beta-alanine and at least one of the glycine, insulin mimic, or insulin-action modifier to the tissue in an amount effective to increase beta-alanylhistidine dipeptide synthesis in the tissue, thereby increasing the anaerobic working capacity in the tissue.

Second Walter Decl. at Ex. L (emphasis added); *see also* claim 2.

Similarly, in U.S. Patent No. 6,680,294 (“the ‘294 patent”), which also claims priority to the ‘596 patent and has an identical disclosure, the inventors obtained claims directed to the administration of dipeptides, including carnosine. *See, e.g.*, ‘294 patent, claim 1 (“providing a methylated analogue of an amino acid selected from the group consisting of **carnosine**, **anserine**, and **balenine**”). (Second Walter Decl. at Ex. M). Carnosine, anserine, and balenine are all dipeptides. Likewise, in the subsequent ‘084 patent, the inventors sought and received claims for a composition and method claims comprising a mixture of creatine and *anserine* or *balenine* (again, **dipeptides**). *See* ‘084 patent, claims 9 and 13. ***Thus, the Petition to Make***

³ The ‘376 and ‘084 patents are attached as Exhibits J and K to the Second Declaration of Keith Walter (“Second Walter Declaration”).

Special could not have been an express disclaimer of dipeptides; the inventors again expressly claimed dipeptides.

The totality of the prosecution history informs the disavowal inquiry. See *Elbex Video, Ltd. v. Sensormatic Electronics Corp.*, 508 F.3d 1366, 1372 (Fed. Cir. 2007) (“[R]ead in isolation, the statement in the prosecution history could be argued to be a disclaimer. When the prosecution history as a whole is considered, the inventor’s response to the PTO is not as clear.”). Here, the sum of the applicants’ statements made throughout the prosecution—including in and after the Petition to Make Special—further compel the conclusion that the inventors did not clearly and unmistakably disavow that their invention encompassed beta alanine in the form of dipeptides such as carnosine.⁴

4. Nothing in the Written Description Suggests That Beta-Alanine and L-Histidine Are Limited to the Individual Amino Acid Form

Plaintiffs’ final argument for limiting beta-alanine and L-histidine to the individual amino acid is that “the written description of the patents-in-suit discloses the use of the individual amino acids β -alanine and L-histidine.” Plaintiffs’ OB at 11 (referring to a single Example in the specification). Plaintiffs fail to acknowledge that the written description acknowledges use of beta-alanine and L-histidine in the form of *both* the individual amino acid and in the form of a component of a dipeptide, and in both cases refers to them as “beta alanine” and “L-histidine.” See Defendants’ OB at 5-6. Thus, the patents’ use of the terms to encompass beta-alanine and L-

⁴ If the Court concludes that the statements made by applicants during the prosecution of the ‘596 patent regarding the *Setra* reference constitute a clear and unmistakable disavowal of beta-alanine and L-histidine as components of dipeptides, which it should not, then that disavowal should only apply to the ‘596 patent in view of the totality of the prosecution history, including applicants failure to abide by their alleged disavowal by subsequently filing and receipt of claims encompassing dipeptides. See *Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003) (holding that when compelled, a court may find that the same claim term in the same patent or related patents carries different meanings).

histidine in the form of the individual amino acid, as well as in the form of components of dipeptides, polypeptides, and oligopeptides, is consistent with Defendants’ construction (and inconsistent with Plaintiffs’). Moreover, Plaintiffs’ argument is legally incorrect: merely because the Example relied upon by Plaintiffs used beta-alanine in individual amino acid form does not mean that the Court should limit the construction of “beta-alanine” to that form. *See Gart v. Logitech, Inc.*, 254 F.3d 1334, 1343 (Fed. Cir. 2001) (it is “well established that broad claims supported by the written description should not be limited in their interpretation to a preferred embodiment”).

As a result, the specification confirms that the terms “beta-alanine” and “L-histidine” are not limited merely to the individual amino acid form, but that they also encompasses beta-alanine and L-histidine as a component of a dipeptide (or other polypeptide). Indeed, only Defendants’ construction is consistent with all the preferred embodiments. *See* Defendants’ OB at 14. Plaintiffs’ construction, on the other hand, would exclude a preferred embodiment. Such a construction is “rarely, if ever, correct.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996).

Thus, because Defendants’ constructions of the terms “beta-alanine” and “L-histidine” conform to the definition provided by the inventors and is consistent with totality of the intrinsic and extrinsic evidence, Defendants’ construction should be adopted.

B. “Dietary Supplement,” If Construed, Should Be Defined as “a Product or Substance That Is Added to the Diet”

NAII’s Proposed Construction	Defendants’ Proposed Construction
“an addition to the normal diet in a pill, capsule, tablet, powder, or liquid form, which is not a conventional food, and effectively increases the function of tissues when consumed”	“a product or substance that is added to the diet”

Under well-established Federal Circuit case law, “dietary supplement” is not a claim limitation. Instead, it is merely a statement of intended use. However, if the Court nevertheless construes the phrase, there is no basis for limiting in the manner proposed by Plaintiffs.

1. “Dietary Supplement” Is Not a Claim Limitation

Plaintiffs contend that phrase “dietary supplement,” which only appears in the preambles of certain claims, should be considered to be a limitation. Plaintiffs are wrong.

The Federal Circuit has recently held that generally, “the preamble does not limit the claims.” *American Medical Systems, Inc. v. Biolitec, Inc.*, 618 F.3d 1354, 1359 (Fed. Cir. 2010) (quoting *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002)). The preamble is not a limitation where the body of a claim sets out the complete invention and the preamble only states a purpose of intended use for the invention. *Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1310 (Fed. Cir. 2002). This is because for apparatus claims, patentability “depends on the claimed structure, not on the use or purpose of that structure.” *Catalina Mktg Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002).

Here, the phrase “dietary supplement” merely states an intended use, and therefore is not a claim limitation. For example, claim 32 of the ‘361 patent claims “A human **dietary supplement** comprising beta-alanine and L-histidine.” (Emphasis added.) The preamble of claim 32, “a human dietary supplement,” is unmistakably an intended use. In addition, the body of claim 32 defines a structurally complete invention setting forth all the limitations of the claimed composition—“comprising beta-alanine and L-histidine.” Nowhere is the phrase “dietary supplement” referenced in the body of the claims. Accordingly, the phrase “dietary supplement” is merely a statement of purposes and is not a limitation.

Plaintiffs contend that the specification “disclose[s] the importance of supplements,” and therefore, that the phrase “dietary supplement” should be treated as a limitation. *See, e.g.*, ‘361

patent, col. 1, lns. 18-25. At most, the specification discusses isolated circumstances (e.g., vegetarian diets or cooking procedures that purportedly reduce beta-alanine, L-histidine, and/or creatine content) in which supplementation may be beneficial. It does not, however, indicate that providing the compositions as a “dietary supplement” is necessary for the invention to achieve its benefits. Accordingly, the term “dietary supplement” does not need to be construed.

2. If “Dietary Supplement” Is Construed, It Should Not Include the Multiple Extraneous Requirements Advocated by Plaintiffs

If the Court construes “dietary supplement,” the Court should reject Plaintiffs’ proposed construction. Plaintiffs argue that the Court should depart from the ordinary meaning of “dietary supplement” advanced by Defendants, and adopt Plaintiffs’ construction, which limits “dietary supplement” to only those dietary supplements that are (1) in “pill, capsule, tablet, powder, or liquid form,” (2) “[effective to] increase the function of tissues,” (3) “consumed,” and (4) not “conventional food.” Plaintiffs proposed construction is not supported by the intrinsic record.

First, it is telling that Plaintiffs provide no argument, let alone intrinsic evidence, to support their position that “dietary supplement” should be limited to a “pill, capsule, tablet, powder, or liquid form” that “effectively increases the function of tissues when consumed.” This is because there is no intrinsic evidence that supports such a construction. For example, the intrinsic evidence makes clear that “dietary supplement” need not be “consumed.” The specification expressly sets forth that dietary supplement can be administered by infusion (e.g., injection), as well as orally, parenterally, or parentally. *See* ‘361 patent, col. 3, lns. 10-11; col. 5, lns. 48-49. The claims of the ‘361 patent further confirm that dietary supplement is not limited to dietary supplements that can be “consumed.” Specifically, claims 9, 21, and 31 of the ‘361 patent, require the dietary supplement to be “in an injectable formulation.” Similarly, claim 4 of the related ‘084 patent reads the dietary supplement “wherein the composition is formulated

for oral, enteral, or parenteral administration.” Second Walter Decl. at Ex. K, claim 4. Likewise, dietary supplements can come in other forms besides pill, capsule, tablet, powder, or liquids, and can have other functions besides “effectively increase[ing] the function of tissues.” For instance, dietary supplements can be taken to lower cholesterol levels.

Second, Plaintiffs argue that the definition of dietary supplement should exclude “conventional foods” such as meat and animal products (which necessarily contain beta-alanine and L-histidine) because such products cannot be used to supplement the diets of vegetarians. Plaintiffs’ OB at 14. Contrary to Plaintiffs’ argument, the intrinsic evidence demonstrates that the inventors did not limit their invention to supplementation directed to only vegetarians. For instance, the inventors explicitly stated that “[t]he methods and compositions can be used to increase beta-alanylhistidine dipeptide by, for example, sportsmen, athletes, body-builders, synchronized swimmers, soldiers, elderly people, horses” ‘361 patent, col. 3, lns. 60-65.

Plaintiffs’ additional argument that “cooking, removes the β -alanine and/or L-histidine from food” is equally unpersuasive. Plaintiffs’ OB at 14. In complete contradiction to Plaintiffs’ contention, the specification describes conventional foods as dietary supplements, and also makes clear that beta-alanine remains in processed (e.g., cooked) foods, in both the individual amino acid form and as a component of dipeptides. In Example 2, the inventors describe supplementing the diets of a test subject with chicken broth, which is a conventional food. ‘361 patent, col. 10, ln. 23 – col. 11, ln. 11 [Example 2]; col. 11, ln. 56 (“broth, a natural food”); *see also, e.g.*, col. 1, lns. 18-20; col. 6, lns. 56-60. In addition, a portion of the chicken broth from Example 2 was assayed for the total beta-alanyl-dipeptide (e.g., carnosine and anserine) and beta-alanine content. *See id.* at col. 10, lns. 43-45. The result of the analysis was that the

chicken broth contained beta-alanine in the individual amino acid form and in the form of a component of dipeptides. *Id.* at lns. 46-52.

This demonstrates that not only do conventional foods, even when cooked, contain beta-alanine (in both the individual amino acid form and as a component of dipeptides), but that the inventors used conventional foods as a dietary supplement in a preferred embodiment.

C. “Active Derivative” Should Be Given the Definition in the Specification

Plaintiffs’ Proposed Construction	Defendants’ Proposed Construction
“a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance, or which is processed into the substance and placed into the body, and excludes dipeptides, oligopeptides and polypeptides”	“a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance, or which is processed into the substance and placed into the body”

Plaintiffs do not dispute that the term “active derivative” is expressly defined in the specification of the patents-in-suit. Nevertheless, Plaintiffs ask the Court to construe this term to exclude active derivatives *derived from* dipeptide, oligopeptide, and polypeptides as well as active derivatives derived from beta-alanine and L-histidine which *are* dipeptides, oligopeptides or polypeptides. Both exclusionary features of Plaintiffs’ construction are without support.

In their brief, Plaintiffs focus on the term “amino acid” and contend that the term is necessarily limited to the individual amino acid form. Plaintiffs’ OB at 15-16. Thus, according to Plaintiffs, “active derivative” means only those derivatives derived from the individual amino acids. Plaintiffs’ construction would exclude esters or amides of dipeptides such as carnosine, and esters or amides of oligopeptides and polypeptides.

In so doing, Plaintiffs seek another bite at the claim construction apple to limit “beta-alanine” and “L-histidine” to only the individual amino acid form.

Plaintiffs again rely on the Petition to Make Special of the ‘596 patent in an effort to support their limiting construction of “active derivative.” However, the ‘596 patent claims do not include the term “active derivative” and applicants’ statements concerning the *Setra* reference had nothing to do with the meaning of “active derivative.” “To the extent that this represents a prosecution disclaimer or prosecution history estoppel argument, it falters on the principle that the prosecution of one claim term in a parent application will generally not limit different claim language in a continuation application.” *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1078 (Fed. Cir. 2005).

Further, the inventors’ definition of “active derivative” includes dipeptides, oligopeptides, or polypeptides that are *derived from* beta-alanine or L-histidine (e.g., carnosine). Yet, Plaintiffs’ construction seeks to expressly exclude such active derivatives. Plaintiffs did not disavow or disclaim the full scope of “active derivative” during patent prosecution.

Finally, Plaintiffs’ last argument seeks to justify the addition of Plaintiffs’ negative sub-limitation (“and excludes dipeptides, oligopeptides and polypeptides”) by providing a *de facto* non-infringement argument. Plaintiffs’ OB at 16. This is wholly improper. The claim construction task is to ascertain the meaning of “active derivative,” not to do what Plaintiffs seek to do, namely, assess whether particular molecules “fit within the meaning of an active derivative that is set forth in the patents in suit” (Plaintiffs’ OB at 16). Thus, “active derivative” should be construed in accordance with the definition set forth in the patents-in-suit.

D. “Unit Dosage Form” Should Be Construed to Have Meaning

Plaintiffs’ Proposed Construction	Defendants’ Proposed Construction
“doses of a certain serving size that can be taken all at once, or in multiple parts throughout the day”	“a form in which a single dose is contained by itself in a single unit”

Plaintiffs’ definition of “unit dosage form” gives no meaning to the term. Plaintiffs contend that the term means “doses of a certain serving size that can be taken all at once, or in multiple parts throughout the day.” However, every compound that is administered for some therapeutic or health benefit has some “dose” associated with it which can be taken all at once or in multiple parts throughout the day. Plaintiffs’ construction gives the fact finder no guidance as to how to identify whether something is provided as a “unit dosage form.”

In contrast, Defendants’ definition—“a form in which a single dose is contained by itself in a single unit”—provides significant guidance to the fact finder. Plaintiffs criticize Defendants’ construction because “the dose sizes disclosed in the written description are not amenable to being contained by itself in a single unit and therefore, must be taken in multiple parts throughout the day.” Plaintiffs’ OB at 19. However, Plaintiffs misleadingly confuse *daily total dosages* set forth in the application with the amount of a *single dose*. In particular, Plaintiffs point to col. 3, lns. 45-49 of the specification and state that “the dose sizes can range from 10 grams to 800 grams,” arguing that it is “not feasible” to provide 800 grams in a single unit. *Id.* However, the specification does not state that 10 grams to 800 grams is the amount of a *single dose*. Instead, it describes this amount as a *total daily dosage*. See ‘361 patent, col. 3, lns. 45-47 (“The composition can be ingested in doses of between about 10 grams and about 800 grams *per day*.”) (emphasis added). As Plaintiffs point out, the specification states that “The [10-800 gram] doses can be administered in one part or multiple parts each day.” See *id.* at col. 3, lns. 48-49. However, Plaintiffs incorrectly suggest that this feature is a mandatory requirement of the claimed invention. Plaintiffs submitted numerous “unit dosage” claims during the prosecution of the ‘084 and ‘294 patents which expressly required far less than 800g, including claims to a “unit dosage” of as little as 100 *milligrams*. See Second Walter Decl. at Ex.

N, 8/13/03 Response and Amendment at 3 (Claims 23-26) and *id.* at Ex. O, 12/5/08 Preliminary Amendment at 4-5 (Claims 9-10 and 23).

Furthermore, the phrase “unit dosage form” appears only in dependent claims, which are necessarily narrower than independent claims, and can thus be more limiting than the specification embodiments. The Court should adopt Defendants’ construction.

E. “Providing an Amount of [Beta-Alanine or L-Histidine] to Blood or Blood Plasma Effective to Increase Beta-alanylhistidine Dipeptide Synthesis in a Human Tissue” Should Not Be Limited to Providing By Ingestion

Plaintiffs’ Proposed Construction	Defendants’ Proposed Construction
“supplying to a human an amount of [beta-alanine or L-histidine] by ingestion and therefore, causing an increase in [beta-alanine or L-histidine] in blood or blood plasma above normal concentrations found in a typical fed state, and thereby increasing the synthesis of beta-alanylhistidine dipeptide in the tissue”	“directly or indirectly providing an amount of [beta-alanine or L-histidine] to the blood or blood plasma that increases beta-alanylhistidine dipeptide synthesis in a human tissue”

There are four fundamental flaws with Plaintiffs’ construction of this phrase. First, the phrase is not limited to any particular mode of “providing,” yet Plaintiffs seek to limit it to “supplying to a human . . . by ingestion.” Second, it adds a brand new intermediate sub-limitation that is not found in the claim language. Third, as with previous limitations, Plaintiffs again seek to use this limitation as a basis for excluding compositions in which beta-alanine or L-histidine are provided in dipeptides, oligopeptides, or polypeptides. Fourth, it adds ambiguity.

Plaintiffs’ Brief completely fails to address its addition of “by ingestion” to its proposed construction of the phrase. Plaintiffs neither explain the basis for adding this term nor provide evidentiary support for it. More importantly, Plaintiffs cannot reconcile their construction with (a) the specification’s clear statement that “[t]he composition can be administered orally, parenterally, or parentrally” (‘361 patent, col. 5, lns. 48-49) and (b) claim 8 of the ‘596 patent,

which embodies the “providing” step and adds “wherein the providing step includes *infusion* of a composition including the amount of beta-alanine.” (Emphasis added.)

The “providing” claim limitation requires only that the specified amount of beta-alanine or L-histidine be provided to the blood or blood plasma. Through the inclusion of “supplying to a human,” Plaintiffs seek to narrow the claim in one aspect while broadening it in another. Plaintiffs’ construction would narrow the ordinary meaning of the claim by requiring that the beta-alanine or L-histidine be supplied to the human by ingestion. Plaintiffs’ construction (in conjunction with its beta-alanine and L-histidine constructions) improperly seeks to exclude the delivery of beta-alanine and L-histidine in the form of components of dipeptides such as carnosine to a human, even though their patents teach that dipeptides are subsequently broken down into their beta-alanine and L-histidine constituents, which are then delivered to the blood or blood plasma (“These precursors [beta-alanine and L-histidine] can be . . . made available via the diet, including from the breakdown of an ingested beta-alanylhistidine dipeptide”). ‘361 patent, col. 5, lns. 12-15. Plaintiffs’ attempt to narrow the scope of their claims in this fashion is flatly inconsistent with the teachings of the patents-in-suit.

Plaintiffs seek to expand their claim scope in another aspect by covering the mere “supplying” of beta-alanine or L-histidine to a human, regardless of whether the compounds are actually provided to the blood or blood plasma. Plaintiffs cite no evidence that supports their attempt to broaden their claim in this fashion.

Plaintiffs’ construction also adds *an entire intermediate limitation*—“causing an increase in [beta-alanine or L-histidine] in blood or blood plasma above normal concentrations found in a typical fed state, and thereby”—to the claim, despite the fact that it is found nowhere in the claim. Plaintiffs again mistakenly rely on the prosecution of the ‘596 patent to support its

construction. However, its reference to *Setra* had nothing to do with this limitation. The prosecution history statement did not concern *how* to provide an effective amount of beta-alanine or L-histidine. Nor did it concern whether “effective amounts” of beta-alanine or L-histidine in the blood or blood plasma are those amounts that exceed “normal concentrations found in a typical fed state.” Thus, the prosecution history argument does not bear on the meaning of this claim term.

The specification further precludes Plaintiffs’ limiting construction. Plaintiffs cite col. 5, lns. 11-20 of the ‘361 patent for the proposition that it excludes the ingestion of carnosine or other dipeptides to increase beta-alanylhistidine levels in muscle tissue because carnosine is part of a “normal diet.” Plaintiffs’ OB at 17. As Plaintiffs point out, the specification states that “in a typical fed state” beta-alanine levels in the muscle tissue limit the amount of beta-alanylhistidine that can be produced in the muscle tissue. ‘361 patent, col. 5, lns. 26-28. Plaintiffs go astray, however, when they then argue that this statement limits its claims to *sources* of beta-alanine that exclude carnosine. The specification says no such thing. Nor does it indicate that carnosine administration cannot elevate beta-alanine levels in the blood or blood sufficiently to raise levels of beta-alanylhistidine in the tissue. To the contrary, Example 2 expressly states that carnosine can be administered to yield the same amount of beta-alanine in the blood plasma as when beta-alanine itself is ingested. *See* ‘361 patent, col. 11, lns. 48-52 (“Administration of carnosine equivalent to 20 milligrams per kilogram body weight of beta-alanine in one test subject resulted in an equivalent increase in the plasma beta-alanine concentration.”). Thus, effective amounts of beta-alanine in the blood plasma may be obtained by administering beta-alanine in the individual amino acid form or as a component of a dipeptide such as carnosine.

Finally, Plaintiffs’ construction introduces unnecessary ambiguity in the claims. Plaintiffs do not cite any evidence from the specification that identifies “normal concentrations” of beta-alanine or L-histidine in blood or blood plasma in a typical fed state. Similarly, what constitutes a “typical” fed state depends greatly on subjective opinion. Plaintiffs’ addition of this language makes their proposed construction highly subjective and unclear. For this reason as well, Plaintiffs’ proposed construction should be rejected. *See, e.g., Datamize LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005) (holding claim indefinite when term “is completely dependent on a person’s subjective opinion”).

F. “Increasing a Concentration of Insulin in the Blood or Blood Plasma” Should Be Given its Ordinary Meaning and Should Not Be Limited to Ingesting or Infusing Insulin or Agents that Stimulate the Production of Insulin

Plaintiffs’ Proposed Construction	Defendants’ Proposed Construction
“the concentration of insulin in the blood or blood plasma is increased by ingesting or infusing insulin, or agents that stimulate the production of insulin”	“directly or indirectly increasing a concentration of insulin in the blood or blood plasma”

This limitation describes a specific effect—increasing a concentration of insulin in the blood or blood plasma. It does not describe or require any particular method for achieving the increase. Nevertheless, Plaintiffs seek to limit the phrase to specific methods, i.e., the ingestion or infusion of insulin-producing agents. Plaintiffs’ argument for its proposed construction relies solely on its reference to two passages of the specification. Plaintiffs’ Brief at 20. However, as Plaintiffs concede, these citations merely indicate that insulin concentrations *can be* increased by ingesting or infusing insulin-producing agents. They do not state or suggest that “increasing a concentration of insulin in the blood or blood plasma” *must* be attained by such ingestion or infusion. Plaintiffs’ proposed definition clashes with a basic principal of claim construction: the

specification cannot be used as a source of claim limitations that do not appear in the claims themselves. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (*en banc*).

Moreover, Plaintiffs' citation to the written description provides that the composition "can include *carbohydrates* (*e.g., simple carbohydrates*), insulin, or agents that stimulate the production of insulin." '361 patent, col. 5, lns. 52-54 (emphasis added). Plaintiffs simply do not address the omission of carbohydrates in their proposed construction. This further supports the rejection of Plaintiffs' construction and the adoption of Defendants' construction.

III. CONCLUSION

For the foregoing reasons, Defendants respectfully submit that their claim constructions be adopted by the Court.

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